APR 15 1999

# Neurospora and the Molecular Revolution

**Norman H. Horowitz**

*Division of Biology, California Institute of Technology, Pasadena, California 91125*

THE molecular revolution that has transformed biology in the last half of the twentieth century began in 1941 with the publication of an article by George Beadle and Edward Tatum describing the first "biochemical mutants" of the bread mold Neurospora (BEADLE and TATUM 1941). This study, revolutionary in its methods and findings, founded modern biochemical genetics and thereby opened a new era in biology. The new discipline grew out of classical genetics, a science in which the genes were treated as mathematical points with the power to replicate themselves, to determine the structure and physiology of the organism in which they reside, to mutate, and to evolve. The means by which these feats were accomplished were unknown in 1941 and were irrelevant for the purposes of classical genetics. In biochemical genetics, however, the concern was precisely with the means by which the genes determine the nature of the organism. This, biochemical genetics showed, was through control of the synthesis of enzymes and other proteins, the rule being that a single gene determines just one specific enzyme (or other protein). This rule became known as the "one-gene-one-enzyme" principle.

These findings constituted the first of three crucial advances that, by 1953, led to molecular genetics. The second was the identification of the genes with DNA. Contrary to the belief almost universally held at the time, genes, it was found, contain no protein in their structure. This finding emerged not from genetics, but, surprisingly, from medical bacteriology. The third, and climactic, discovery showed that DNA is a linear, self-complementary, double-helical polynucleotide—a structure that immediately suggested how genes replicate, mutate, and determine the structure of proteins.

Starting from these discoveries, the science of biology has attained previously unknown depths of understanding of the operation, evolution, and origin of living matter. New sciences, new technologies, and new industries have arisen from them.

Even before the advent of molecular genetics in 1953, the biochemical genetics of Neurospora had had a profound effect on the biological sciences. First was the unification of genetics and biochemistry. Genetics, a subject that up to then had been notably isolated from the physical sciences suddenly found itself in the mainstream of biochemistry. In what at the time was a genuine cultural revolution, papers dealing with mutants of *Neurospora crassa* began to appear in the pages of *The Journal of Biological Chemistry*. These papers brought proof beyond question that metabolism is an expression of gene activity, a principle that is now axiomatic, but that at the time caused astonishment.

Another major consequence of Beadle and Tatum's article was the introduction of microorganisms into genetical research. Neurospora is a microorganism (so classified, along with all other fungi, because it is normally propagated from single somatic cells), and it is also a eucaryote, an organism whose chromosomes are contained in nuclei. Soon after publication of the 1941 Neurospora paper, Tatum found that the same kind of mutations that he and Beadle had obtained in Neurospora could be induced also in bacteria, which are procaryotes (cells without a nuclear membrane). These mutations made possible a renewed search for mating and genetic recombination in bacteria, a search that had been attempted unsuccessfully by earlier investigators using inadequate markers. There were serious questions at the time as to whether bacteria had genes comparable to those of higher plants and animals. Now they were found, and bacterial genetics, a new and important branch of biology, was launched.

A third major legacy of the Neurospora investigations is summed up in the generalization one-gene-one-enzyme, the idea that genes carry information regarding the production of enzymes and that the relation is a simple one: a single gene determines the existence and properties of one enzyme (or other protein). For proteins made up of more than one kind of polypeptide chain, each polypeptide chain is determined by its own gene. This principle has long seemed to me to be the key to understanding the organization of living matter: it states that the genetic part of the organism—the part that is transmitted from generation to generation, known now not to be protein—consists of instructions for the synthesis of proteins; these latter are responsible for the construction and operation of the organism. This insight, together with the implied mechanisms, has been called "[p]robably the most important discovery ever made in biology" (DIXON and WEBB 1979).

One can see now that the one-gene-one-enzyme principle was foreshadowed in research dating back to the early part of the century, but it is incorrect to suggest (as Beadle himself did, in a characteristically generous gesture in his Nobel Address) that the Neurospora findings merely rediscovered what others had already known. If this had been true, the Neurospora results would not have been greeted with the astonishment that met them wherever they were described. In actuality, there was no other body of data bearing on the problem of gene action that could compare in quantity and quality with that built up on the Neurospora mutants and certainly no other that could support the weight of the one-gene-one-enzyme theory.

Today, nearly 60 years after publication of the article by Beadle and Tatum, Neurospora no longer occupies the position it formerly held as the one microorganism with a rich and well-understood genetics. For many problems, bacteria and yeast are now the preferred experimental organisms. Neurospora nevertheless continues to be a source of inspiration and discovery for geneticists, just as it was for the author in the forties, when he worked in Beadle's laboratory, and every day brought exciting discoveries and fresh insights into what was to be a new science.

## LITERATURE CITED

BEADLE, G. W., and E. L. TATUM, 1941 Genetic control of biochemical reactions in Neurospora. Proc. Natl. Acad. Sci. USA **27:** 499–506.

DIXON, M., and E. C. WEBB, 1979 *Enzymes*, pp. 570–571. Academic Press, New York.